

DRAFT PACKAGE INSERT

DESCRIPTION

GlucaGen® [glucagon (rDNA origin) for injection] manufactured by Novo Nordisk A/S is produced by expression of recombinant DNA in a *saccharomyces cerevisiae* vector with subsequent purification.

The chemical structure of the glucagon in GlucaGen® is identical to naturally occurring human glucagon and to glucagon extracted from beef and pork pancreas. Glucagon with the empirical formula of $C_{153}H_{225}N_{41}O_{47}S$, and a molecular weight of 3483, is a single-chain polypeptide containing 29 amino acid residues. The structure of glucagon is:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-
1 2 3 4 5 6 7 8 9 10 11

Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
12 13 14 15 16 17 18 19 20 21 22

Val-Gln-Trp-Leu-Met-Asn-Thr
23 24 25 26 27 28 29

GlucaGen® 1 mg (1 IU) is supplied as a sterile, lyophilized white powder in a 2 ml vial, accompanied by Sterile Water for Reconstitution (1 ml) also in a 2 ml vial. Glucagon, as supplied at pH 2.5-3.5, is soluble in water.

Active Ingredient in each vial

Glucagon as hydrochloride 1 mg (corresponding to 1 IU).

Other Ingredients

Lactose monohydrate (107 mg)

When the glucagon powder is reconstituted with Sterile Water for Reconstitution, it forms a solution of 1 mg (1 IU)/ml glucagon for subcutaneous (sc), intramuscular (im), or intravenous (iv) injection.

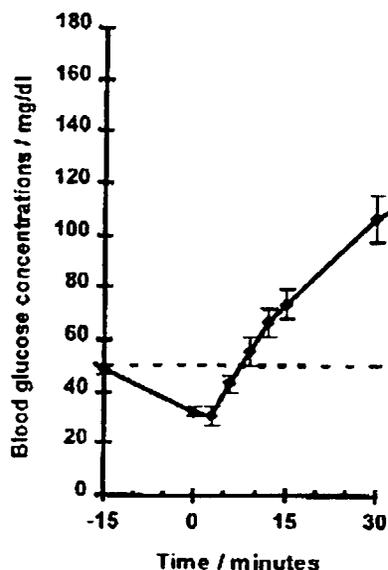
GlucaGen® is an antihypoglycemic agent, and a gastrointestinal motility inhibitor.

CLINICAL PHARMACOLOGY

Intramuscular (IM) injection of GlucaGen® resulted in a mean C_{max} (CV%) of 1686 pg/ml (43%) and median T_{max} of 12.5 minutes. The mean apparent half-life of 45 minutes after IM injection probably reflects prolonged absorption from the injection site. Glucagon is degraded in the liver, kidney, and plasma.¹

Antihypoglycemic Action: Glucagon induces liver glycogen breakdown, releasing glucose from the liver. Blood glucose concentration rises within 10 minutes of injection and maximal concentrations are attained at approximately a half hour after injection (see Figure). Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect.

Recovery from insulin induced hypoglycemia (mean blood glucose) after i.m. injection of 1 mg GlucaGen® in Type 1 diabetic men



Gastrointestinal Motility Inhibition: Extra hepatic effects of glucagon include relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon.

INDICATIONS AND USAGE

For the treatment of hypoglycemia: GlucaGen® is used to treat severe hypoglycemic (low blood sugar) reactions which may occur in patients with diabetes treated with insulin. Because GlucaGen® depletes glycogen stores, the patient should be given supplemental carbohydrates as soon as he/she awakens and is able to swallow, especially children or adolescents.

Medical evaluation is recommended for all patients who experience severe hypoglycemia.

For use as a diagnostic aid: GlucaGen® is indicated for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract. Glucagon is as effective for this examination as are the anticholinergic drugs. However, the addition of the anticholinergic agent may result in increased side effects.

CONTRAINDICATIONS

Glucagon is contraindicated in patients with known hypersensitivity to glucagon or any constituent in GlucaGen® and in patients with pheochromocytoma or with insulinoma.

WARNINGS

GlucaGen® should be administered cautiously to patients suspected of having pheochromocytoma or insulinoma. Secondary hypoglycemia may occur and should be countered by adequate carbohydrate intake following glucagon treatment.

Glucagon may release catecholamines from pheochromocytomas and is contraindicated in patients with this condition.

Allergic reactions may occur and include generalized rash, and in rare cases anaphylactic shock with breathing

difficulties, and hypotension. The anaphylactic reactions have generally occurred in association with endoscopic examination during which patients often received other agents including contrast media and local anesthetics. The patients should be given standard treatment for anaphylaxis including an injection of epinephrine if they encounter respiratory difficulties after GlucaGen® injection.

PRECAUTIONS

General-In order for GlucaGen® treatment to reverse hypoglycemia, adequate amounts of glucose must be stored in the liver (as glycogen). Therefore, GlucaGen® should be used with caution in patients with conditions such as prolonged fasting, starvation, adrenal insufficiency or chronic hypoglycemia because these conditions result in low levels of releasable glucose in the liver and an inadequate reversal of hypoglycemia by GlucaGen® treatment. Caution should be observed when glucagon is used in diabetic patients or in elderly patients with known cardiac disease to inhibit gastrointestinal motility.

Information for Patients - Refer patients and family members to the Information for Patients for instructions describing the method of preparing and injecting GlucaGen®. Advise the patient and family members to become familiar with the technique of preparing glucagon before an emergency arises. Instruct patients to use 1 mg for adults or ½ the adult dose (0.5 mg) for children weighing less than 55 lb (25 kg). To prevent severe hypoglycemia, patients and family members should be informed of the symptoms of mild hypoglycemia and how to treat it appropriately. Family members should be informed to arouse the patient as quickly as possible because prolonged hypoglycemia may result in damage to the central nervous system. Patients should be advised to inform their physician when hypoglycemic reactions occur so that the treatment regimen may be adjusted if necessary.

Laboratory Tests-Blood glucose measurements may be considered to monitor the patients response.

Carcinogenesis, Mutagenesis, Impairment of Fertility-

Long term studies in animals to evaluate carcinogenic potential have not been performed. Several studies have been conducted to evaluate the mutagenic potential of glucagon. The mutagenic potential tested in the Ames and human lymphocyte assays, was borderline positive under certain conditions for both glucagon (pancreatic) and glucagon (rDNA) origin. *In vivo*, very high doses (100 and 200 mg/kg) of glucagon (both origins) gave a slightly higher incidence of micronucleus formation in male mice but there was no effect in females. The weight of evidence indicates that GlucaGen® is not different from glucagon pancreatic origin and does not pose a genotoxic risk to humans.

GlucaGen® was not tested in animal fertility studies. Studies in rats have shown that pancreatic glucagon does not cause impaired fertility.¹

Pregnancy-Pregnancy Category B-Reproduction studies were performed in rats and rabbits at GlucaGen® doses of 0.4, 2.0, and 10 mg/kg. These doses represent exposures of up to 100 and 200 times the human dose based on mg/m² for rats and rabbits, respectively, and revealed no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers-It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GlucaGen® is administered to a nursing woman.

No clinical studies have been performed in nursing mothers, however, GlucaGen® is a peptide and intact glucagon is not absorbed from the GI tract. Therefore, even if the infant ingested glucagon it would be unlikely to have any effect on the infant. Additionally, GlucaGen® has a short plasma half life thus limiting amounts available to the child.

Pediatric Use- For the treatment of hypoglycemia: The use of glucagon in pediatric patients has been reported to be safe and effective.^{2,3,4,5}

For use as a diagnostic aid: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Severe side effects are very rare, although nausea and vomiting may occur occasionally especially with doses above 1 mg or with rapid injection (less than 1 minute).¹ Glucagon exerts positive inotropic and chronotropic effects (tachycardia). Adverse reactions indicating toxicity of GlucaGen® have not been reported. A transient increase in both blood pressure and pulse rate may occur following the administration of glucagon. Patients taking B-blockers might be expected to have a greater increase in both pulse and blood pressure, an increase of which will be transient because of glucagon's short half-life. The increase in blood pressure and pulse rate may require therapy in patients with pheochromocytoma or coronary artery disease. (see OVERDOSAGE).

Allergic reactions may occur in rare cases. (See WARNINGS).

OVERDOSAGE

Signs and Symptoms-No reports of overdosage with GlucaGen® have been reported. It is expected, if overdosage occurred, that the patient may experience nausea, vomiting, inhibition of GI tract motility, increase in blood pressure and pulse rate.¹ In case of suspected overdosing, the serum potassium may decrease and should be monitored and corrected if needed.

The IV and SC LD₅₀ for GlucaGen® in rats and mice ranges from 100 to greater than 200 mg/kg body weight.

Treatment- Standard symptomatic treatment may be undertaken if overdosage occurs. If the patient develops a dramatic increase in blood pressure, 5 to 10 mg of phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed. It is unknown whether GlucaGen® is dialyzable, but such a procedure is unlikely to provide any benefit given the short half-life and nature of the symptoms of overdose.

DOSAGE AND ADMINISTRATION

GlucaGen® should be reconstituted with the supplied 1 ml of Sterile Water for Reconstitution.

Draw up all of the Sterile Water for Reconstitution with syringe and inject into the GlucaGen® vial. Roll the vial gently until powder is completely dissolved and no particles remain in the fluid. The reconstituted fluid should be clear and of water-like consistency. The reconstituted GlucaGen® gives a concentration of approximately 1 mg/ml Glucagon. The reconstituted GlucaGen® should be used immediately after reconstitution.^{5*} Discard any unused portion.

For the treatment of hypoglycemia: For adults and for pediatric patients weighing 55 lb (25 kg) or more, administer 1 mg by subcutaneous, intramuscular, or intravenous injection.^{1,6} According to the literature, ½ adult dose (0.5 mg) is recommended for pediatric patients weighing less than 55 lb (25 kg) or younger than 6-8 years old.^{2,3,4,5,6} Emergency assistance should be sought if the patient fails to respond within 15 minutes after subcutaneous or intramuscular injection of glucagon. The glucagon injection may be repeated while waiting for emergency assistance.¹ Intravenous glucose MUST be administered if the patient fails to respond to glucagon. When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent recurrence of hypoglycaemia.

Directions for Use as a Diagnostic Aid: Reconstitute as indicated above. Discard any unused portion.

Time of maximal glucose concentration

Intravenous: 5 to 20 minutes

Intramuscular: 30 minutes

Subcutaneous: 30 to 45 minutes

Time for GI smooth muscle relaxation¹

Intravenous: 0.25 to 2 mg (IU) - 45 seconds.

Intramuscular:

1 mg (IU) - 8 to 10 minutes

2 mg (IU) - 4 to 7 minutes

Duration of action -

Hyperglycemic action - 60 to 90 minutes

Smooth muscle relaxation -¹

Intravenous:

0.25 to 0.5 mg (IU) - 9 to 17 minutes

2 mg (IU) - 22 to 25 minutes

Intramuscular:

1 mg (IU) - 12 to 27 minutes

2 mg (IU) - 21 to 32 minutes

STABILITY AND STORAGE

Before Reconstitution: The GlucaGen® package should be kept refrigerated between 2° and 8° C (36° and 48° F) until the expiration date. Avoid freezing and protect from light. The GlucaGen® package may be stored up to 12 months at room temperature 20° to 25° C (68° to 77° F) prior to reconstitution. GlucaGen® should not be used after the expiry date on the vials.

After Reconstitution: Reconstituted GlucaGen® should be used immediately. Discard any unused portion. If the solution shows any sign of gel formation or particles, it should be discarded.

HOW SUPPLIED

GlucaGen® Diagnostic Kit includes:

1 vial containing 1 mg (1 IU) GlucaGen® [glucagon (rDNA origin) for injection]

1 vial containing 1ml Sterile Water for Reconstitution

NDC 0169-7065-12

GlucaGen® Emergency Kit for low blood sugar includes:

1 vial containing 1 mg (1 IU) GlucaGen® [glucagon (rDNA origin) for injection]

1 vial containing 1 ml Sterile Water for Reconstitution

Disposable syringe and needle

NDC xxxx-xxxx-xx

Rx only

Edition Date: June 22, 1998

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